Title that I was Given
Development and Maturation of the Lung: Age-Specific Vulnerabilities

Ira B. Tager, M.D, M.P.H.
School of Public Health
UC Berkeley

Title Which I Prefer

Importance of Early Life Environmental Exposures on the Respiratory Health of Children

A Bit of Perspective

- "Pulmonary factors" which are associated with the severity of childhood asthma
  - lowered levels of lung function
  - a high degree of airways hyperreactivity
- "Pulmonary factors" which are associated with the persistence of childhood asthma into adulthood
  - lowered levels of lung function
  - a high degree of airways hyperreactivity

Stages of Human Lung Growth

From: Thurlbeck W.

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Timetable of Development of Lung During Fetal Life

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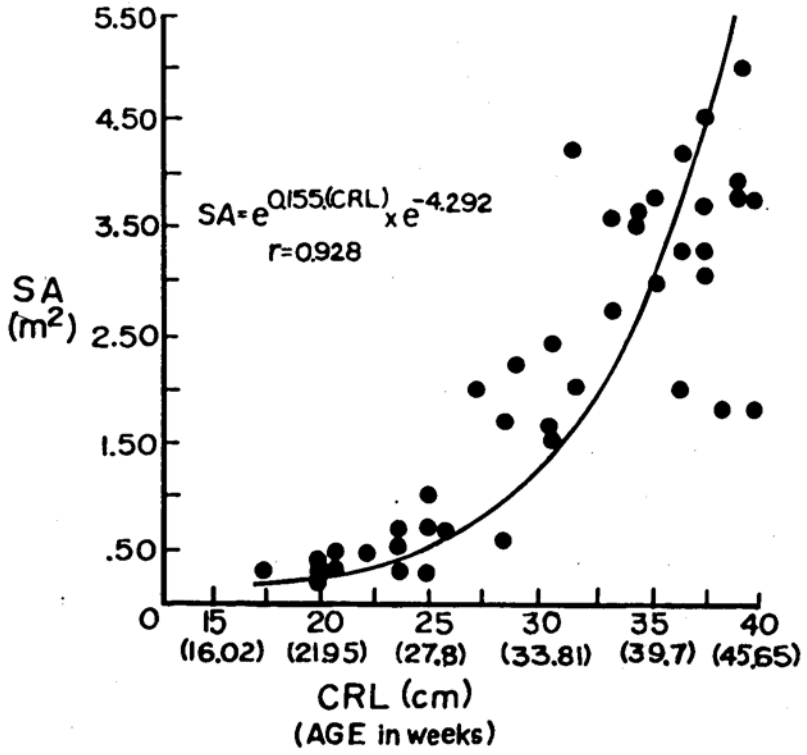
Relation Between Gas-Exchanging Surface Area and Age and Crown-Rump Length

From: Langston, C, *et al.*, 1984



Number of Alveoli Between Respiratory Bronchioles and Periphery of Acinus Represented by Point Count

From: Thurlbeck W, 1982

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Post-Natal Development of Alveoli from Age 1 Month to 8 years

From: Thurlbeck W, 1982

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"Growth" of FEV_1 from Childhood

From: Tager IB, *et al.*

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Childhood Respiratory Health Outcomes

- Growth of lung function
- Airways hyper-reactivity
- Atopic allergy
- Respiratory Symptoms and Specific Illnesses
  - wheezing
  - cough
  - acute respiratory illness (e.g., viral)
  - asthma

Environmental Exposures Which May Exert Effects During Fetal Development or Within the First Few years of Life

- Tobacco smoke
  - *in utero exposure*
  - post-natal passive exposure
- Ambient air pollution
- Aero-allergens

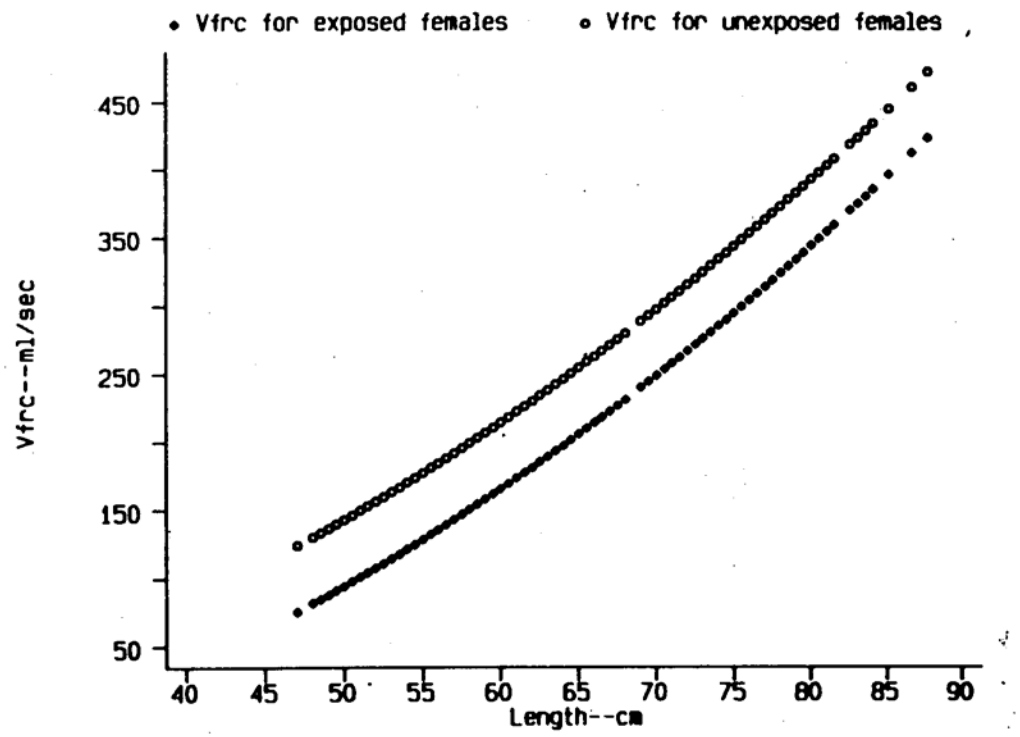
Timing of Effects of *in utero* Exposure to Tobacco Smoke Products on Respiratory Function in Pre-Term Infants

Measure of Function	Maternal Smoking	No Maternal Smoking
$Vmax_{FRC}$ ml/sec	85 ✂42	104 ✂50
$T_{PTEF} : T_E$	0.37 ✂0.11	0.43 ✂0.14

From: Hoo A-F, *et al*., 1998

Effects of Maternal Smoking *in utero* and Early Post-natal Period on Lung Function Growth --First 18 Months

From: Tager IB, *et al., 1995*



$Vmax_{FRC}$ (ml/sec) In Relation to History of Wheezing over the First Six Years of Life

Age	No Wheezing	Transient Early Wheezing	Persistent Wheezing
<1 yr	123 (110-138)	71 (52-94)	105 (74-145)
6 yrs	1262 (1217-1308)	1098 (1035-1164)	1070 (907-1146)

From: Martinez F, *et al*. NEJM, 1995

Relationship Between Lung Function and the Occurrence of Wheezing Lower Respiratory Illness in the First Year of Life

Pulmonary Function Measure	No LRI After PF	LRI After PF
FRC, ml/cm		
Males	1.65 ± 0.09	1.72 ± 0.07
Females	1.58 ± 0.09	1.59 ± 0.07
V_{FRC}, ml/sec/cm		
Males	2.32 ± 0.29	2.06 ± 0.20
Females	2.91 ± 0.26	2.38 ± 0.20

From: Tager IB, *et al*., 1993

Effect of Maternal Smoking on Mid_Expiratory Flow Rates Birth to Age 18 Years--Six Cities Data

From: Wang X, *et al*., 1994

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Associations Between Birth Weight and Markers of Respiratory Health

- Decreasing Birth Weight Associated with:
  - Occurrence of asthma
  - Occurrence of wheeze
  - Altered respiratory mechanics at birth
  - Occurrence and mortality from COPD in adult life
  - lowered forced expiratory volumes in adult life

Relationship Between IUGR and PM Exposure During Pregnancy

	PM_{10} 40 to < 50µg/m^3	PM_{10} > 50µg/m^3
Month of Gestation	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**
1	1.62 (1.07-2.50)	2.64 (1.48-4.71)
3	1.02 (0.68-1.54)	0.87(0.51-1.47)
5	0.92 (0.62-1.36)	0.82 (0.48-1.39)
7	0.83 (0.57-1.21)	0.83 (0.49-1.42)
9	1.03 (0.70-1.52)	1.25 (0.73-2.12)

From: Dejmek J, *et al*., Environ Health Perspect, 1999

Effect of Birth Weight and Prematurity on Response to 15 ppb Increase in Ambient O_3 In Children with Asthma--NCICAS

	% PEF_{AM}		Incidence of Morning Symptoms	
	%Change	95%CI	OR	95% CI
Normal Birth Weight and Full Term	-0.30	-0.79 to 0.19	1.09	0.95 to 1.24
Low Birth Weight or Premature	-1.83	-2.65 to –1.01	1.42	1.10 to 1.82

From: Mortimer KM, *et al*. Submitted for publication

Effect of Level of Lung Function on Airways Reactivity in Infants

- Study of 154 infants (average age 180 days at testing)
- Adjust $Vmax_{FRC}$/length for:
  - ETS exposure
  - molds in household
  - gas stove
  - presence of RSV infection
  - maternal/paternal history of asthma and atopy
- Evaluate dose response slope
  - adjusted still significant predictor of PC_{40} to histamine

Omit slide 22

Relative Importance of Factors Which Negatively Impact Growth of FEF_{25-75} in Children and Adolescents

Factor	Effect on $\ln(FEF_{25-75})$ Liters/Minute Mean (se)
Current personal smoking	-0.020 (0.015)
Maternal smoking	-0.028 (0.008)
Airway reactivity at all test	-0.067 (0.026)
Airway reactivity at some tests	-0.025 (0.010)

From: Redline S, *et al*., 1989

Bronchial Reactivity at Age 6 Years and Risk of Subsequent Asthma

From: Lombardi E, *et al*., 1997

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Omit slide 25

Effect of Atopic Status on Change in FEV_1 % Predicted Between Ages 12-19 Years

Factor	Direction of Effect on FEV_1 % Predicted
☯Antecedent FEV_1	positive
Antecedent asthma	negative
New onset asthma	negative
☯reactivity to histamine	negative
New onset of *allergy to HDM*	negative

From: Ulrik CS, *et al*. AJRCCM, 1999

Predictors of Wheeze in the First Year of Life in Children at High Risk for Atopy

Predictor	RR for Wheeze Compared with Baseline Category of Factor
Cockroach antigen in dust ≥5 U/g	1.8 (1.2-2.6)
Lower respiratory illness (yes)	2.3 (1.6-3.2)
Smoking during pregnancy (yes)	1.8 (1.1-3.0)
Low birth weight (per 0.61 kg)	1.3 (1.0-1.6)
Maternal asthma (active)	1.4 (0.9-2.0)
Dog in home (yes)	1.3 (0.9-2.0)

From: Gold DR, *et al*. AJRCCM, 1999

Cytokine Profiles at Age Two Years in Atopic and Non-Atopic Children

From: Prescott, SL, *et al*., 1999

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Process of Immune Deviation

From: Holt P, *et al*., 1997

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Ontogeny of Atopy: Failure of Immune Deviation

Adapted, in part, from Holt and Colleagues

- Initial T-cell priming commonly occurs to antigens to which mother exposed during 3rd trimester
  - cytokine profile of this response is Th2-polarized ("atopic" phenotype)
- Non-atopic infants show age-dependent declines in Th2 cytokines which is not seen in persons who become atopic
- Failure of immune deviation is associated with ॐproduction of ☎-interferon
  - greatest in infants at greatest genetic risk for atopy
- Environmental factors that inhibit immune deviation could enhance a genetic risk of atopy

Effects of Diesel Exhaust Particles on Human Immune Responses

- In already sensitized subjects
  - increased IgE production to mucosal antigens
    - increase number of IgE producing cells
    - enhanced isotype switching to IgE production
  - skewing of cytokine pattern to Th2 phenotype
  - inhibition of ☎-interferon
- Skewing of immune response to Th2 phenotype in non-sensitized individuals

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Conclusions

- Environmental exposures that occur during fetal life and during the first few years of life have been shown to adversely effect lung function development
  - subtle alterations in growth of the lung and its attendant mechanical properties probably are an underlying risk factor for
    - the occurrence of chronic childhood respiratory disease
    - the severity of childhood respiratory disease

Conclusions

- Alterations in lung function influence the occurrence and perhaps severity of airways hyper-reactivity (AHR)
  - AHR itself is a marker for altered lung function
- Children who are atopic have slower lung function development
  - atopy is the major source of the pulmonary inflammatory reaction that characterizes childhood asthma
- The development of the atopic state may be enhanced by non-allergen environmental exposures
  - such exposures may in turn enhance the exposure to allergen